Description

Method and arrangement and computer program with program code means and computer program product for the analysis of neuronal activities in neuronal areas

The invention relates to an analysis of neuronal activities in neuronal areas, for example of nerve structures in areas of the brain of a patient.

Knowledge about a mode of operation of a neuronal area and about an interaction of neuronal areas are fundamental to functional nuclear spin tomography or fMRI technology [3], which is a further development of the known magnetic resonance tomography.

Previously known magnetic resonance tomography (also nuclear spin tomography, abbreviated to MR) is an imaging method which produces sectional images of the human body without using damaging X-rays.

Instead MR takes advantage of the behavior of body tissue in a strong magnetic field. Pathological changes in body tissue, for example in the brain or spinal cord, can be detected by this means.

Functional disorders in body tissue, particularly in the brain of a patient, cannot, however, be detected by means of conventional magnetic resonance tomography.

This is performed by functional nuclear spin tomography or fMRI technology.

The neuronal activity in areas of the brain of a patient can be measured indirectly by means of the fMRI technique. The BOLD (Blood Oxygenation Level Dependent) signal, as it is called, is measured in individual areas of the brain, said signal relating to neuronal activity in the respective areas.

Dependencies, which stem among other things from structures in the brain, i.e. from neuronal links between nerve cells or nerve structures, exist between the neuronal activities in the areas.

The outcome of the fMRI measurements shows the course of activity of individual areas over a certain period, for example during cognitive sequences as a result of specific perception processes or motor tasks.

Functional disorders, in this case in the brain, are thus implicitly contained in the fMRI signals measured.

Efficient methods for the analysis and evaluation of such fMRI measurements are thus desirable in order to be able to furnish evidence of possibly existing functional disorders in specific areas.

Previously known methods, such as for example the method of analysis known from [6], are restricted to a detection of functional relationships between various areas of the brain in certain predetermined tasks such as the aforementioned perception processes or motor tasks (functional connectivity). These functional relationships are also designated functional connectivity.

In contrast to functional connectivity, however, the determination of a true physical connectivity, i.e. the determination of actually existing linking structures (of areas of the brain) independently of specific predetermined tasks, is not possible with these known methods.

A further known method of analysis for detecting functional connectivity is described below.

The object of this known method of analysis described below is the above-described detection of functional relationships between

various areas of the brain in specific perception processes or motor tasks.

This known method of analysis is based upon a predefined model of a brain, i.e. a predefined brain architecture.

This brain architecture, predetermined *a priori* from prior knowledge, defines general functional and/or spatial dependencies between specific areas of the brain in the form of a coupling matrix S, as it is called.

The coupling matrix S has a form or structure fixed in accordance with the predetermined brain architecture (columns/rows) and is accordingly populated in certain, but not at all (matrix) positions with changeable coupling strengths S_i. These are changeable and are matched as part of the method of analysis.

The unpopulated (matrix) positions are populated with fixed, unchangeable values, namely zero.

The coupling strengths S_i describe functional dependencies respectively between two areas of the brain or the BOLD signals measured there and representing the neuronal activities there.

In this known method of analysis, the (changeable) coupling strengths S_i are now defined such that statistical characteristic quantities which are determined by this method of analysis from the fMRI measurements, can best be explained. Expressed differently, a probability for an occurrence of the measured data, i.e. the fMRI measurement or the BOLD signals, is to be maximized by means of the desired coupling strengths S_i.

In this method of analysis a data point $s=s_t$ represents a totality of all BOLD signals s1, ..., sN of the individual n areas at a point in time t or averaged over a time interval t (t=[1;T]).

The fMRI measurement comprises a large number of such data points for possibly differing perception processes and/or motor tasks, for which the corresponding BOLD signals were measured.

In the known method of analysis, it is now not the individual data points s1, s2, ..., sT which are evaluated directly but statistical characteristic quantities which emerge from these.

For a statistical distribution of the data points s1, s2, ..., sT it is assumed that it is described fully by a multivariant normal distribution, i.e. a statistical distribution of the first order, with a mean value μ and a covariance Σ:

$$P(s \mid \mu, \Sigma) = \frac{1}{\sqrt{2\pi}^{N} \bullet |\Sigma|} \bullet e^{-\frac{1}{2}(s-\mu)' \Sigma^{-1} (s-\mu)} \qquad (1)$$

For sufficiently long series of measurements, the occurrence of the individual data points si of s1, s2, ..., sT can be viewed as statistically independent.

The probability P=P(s1, ..., sT$\mid \mu, \Sigma$) for an occurrence of all measured data points s1, ..., sT can accordingly be written as:

$$P(s_1,...,s_T \mid \mu, \Sigma) = \prod_{t=1}^{T} P(s_t \mid \mu, \Sigma) =$$

$$= \frac{1}{\sqrt{2\pi}^{NT} \bullet |\Sigma|^{T}} \bullet e^{-\frac{1}{2}\sum_{t=1}^{T}(s_t-\mu)' \Sigma^{-1} (s_t-\mu)} \qquad (2)$$

Here, the unknown variables, the mean value μ and the covariance Σ, depend exclusively on a(brain)model which describes the measured data.

The model assumes a linear statistical relationship between the individual BOLD signals:

$$s_i = \sum_{j=1}^{N} S_{ij} s_j + \varepsilon_i \quad \text{for } i = 1, \ldots, N$$

or

$$s = Ss + \varepsilon \qquad (3)$$

where ε describes the external influence on the individual BOLD signals, like a sensory input of sensory cells on the examined areas of the brain.

The influence variables εi and εj on different examined areas i and j may in this case be correlated throughout.

The model parameters to be specified are consequently the coupling strengths S_i of the underlying coupling matrix S, the mean value με of the external influence ε and the covariance Σε of ε.

The mean value μ and the covariance Σ depend on these:

$$\mu = \mu(S, \mu_\varepsilon)$$

$$\Sigma = \Sigma(S, \Sigma_\varepsilon) \qquad (4)$$

In the known method of analysis the model parameters are then determined such that the probability P=P(s1, ..., sT| μ,Σ) given in (2) for the occurrence of the measured data is maximized.

For this purpose, a known maximum likelihood estimation [1] method (optimization) is applied.

Using the relationships (4) in (2), an expression that is dependent on the coupling strengths S_i, the mean value με and the covariance Σε is obtained, which expression is maximized by the optimization.

The optimization then leads to the desired coupling strengths S_i between the BOLD signals.

These in turn then enable detection of functional relationships between various areas of the brain in specific perception processes or motor tasks (functional connectivity).

The known method of analysis described hereinabove exhibits the disadvantage, however, that the measured fMRI signals are explicable only insufficiently accurately or that the model is matchable only insufficiently accurately to the measured fMRI signals and consequently the mode of operation or interaction of neuronal areas is only insufficiently mappable. This shortcoming could possibly lead to incorrect conclusions being drawn with regard to connective functionality.

A software tool for an fMRI method of analysis, an "fmri.pro", is known from [4]. A device for implementing the fMRI technique is known from [5].

The object of the invention is consequently to indicate an improved method of analysis for the analysis of neuronal activities. The improved method of analysis is intended to be able to better explain measured fMRI signals and thereby to better describe the mode of operation and interaction of neuronal areas than is the case with the above known method of analysis.

This object is achieved in the method and the arrangement and in the computer program with program code means and in the computer program product for the analysis of neuronal activities in neuronal areas having the features according to the respective independent Claim.

In the method for the analysis of neuronal activities in neuronal areas using signals describing the neuronal activities, the signals are determined, whereby each signal describes the neuronal activity in one of the neuronal areas.

A matchable coupling which is described by using matchable coupling variables which describe a statistical relationship between the matchably coupled signals forms the basis of all the signals, not just some of them.

Probabilities for an occurrence of the signals are determined, whereby a statistical distribution forms the basis of the occurrence of the signals.

All matchable coupling variables are determined by an optimization of the probabilities and hence matched.

The neuronal activities are analyzed using the matchable coupling variables.

The arrangement for the analysis of neuronal activities in neuronal areas by the use of signals describing the neuronal activities has units standing functionally in contact with one another and which are configured such that

- the signals can be determined, whereby each signal describes the neuronal activity in one of the neuronal areas,
- a matchable coupling can form the basis of all, not just some of the signals, said matchable coupling being described by using matchable coupling variables which describe a statistical relationship between the matchably coupled signals,
- probabilities for an occurrence of the signals can be determined, whereby a statistical distribution forms the basis of the occurrence of the signals,
- all matchable coupling variables can be determined by an optimization of the probabilities and hence matched,
- the neuronal activities can be analyzed using matchable coupling variables.

It is essential to the invention that the matchable coupling which is described by using the matchable coupling variables forms the basis of all signals. By this means, absolutely all coupling

variables are determined by the optimization of probabilities and hence matched.

In this way the invention differs from the known method of analysis described hereinabove in that in the known method of analysis matchable statistical coupling forms the basis of only some of the signals.
Only these can be determined by means of the optimization of probabilities and hence matched.

Seen clearly, the known method of analysis thus presupposes a known, predetermined and stipulated neuronal structure.

In contrast to this, no predetermined and fixed coupling structures are assumed in advance by the inventive approach. These emerge only within the context of the optimization.

Through the interaction of an optimization method and a search method, i.e. the search for existing couplings and the determination of their optimum values, in the inventive approach both the coupling structure most probable on the basis of the signals and a coupling strength of the specific couplings are determined.

A particularly advantageous aspect of the inventive approach is that this approach is independent of other methods and of possibly defective prior knowledge. No prior knowledge, or just outline prior knowledge, of coupling structures is needed in the case of the invention in order to analyze the neuronal activities.

As a result of the flexibility achievable by the invention in the matching of couplings, neuronal structures can be determined with greater precision and in greater detail.

The computer program with program code means according to the invention is equipped to perform all steps in accordance with the

method of analysis according to the invention if the program is run on a computer.

The computer program product with program code means stored on a machine-readable medium is equipped to perform all steps in accordance with the method of analysis according to the invention if the program is run on a computer.

The arrangement and the computer program with program code means which are equipped to perform all the steps in accordance with the inventive method of analysis if the program is run on a computer and the computer program product with program code means stored on a machine-readable medium which is equipped to perform all the steps in accordance with the inventive method of analysis if the program is run on a computer are particularly suitable for performing the method of analysis according to the invention or one of its further developments explained hereinbelow.

Preferred further developments of the invention will emerge from the dependent claims.

The further developments described hereinafter relate both to the methods and to the arrangement.

The invention and the further developments described hereinafter can be implemented both in software and in hardware, for example using a special electrical circuit.

Furthermore, implementation of the invention or of a further development described hereinafter is possible by means of a computer-readable storage medium on which is stored the computer program with program code means which executes the invention or further development.

The invention or each further development described hereinafter can also be implemented in a computer program product which has a

storage medium on which is stored the computer program with program code means which executes the invention or further development.

The statistical distribution which forms the basis of the occurrence of the signals can be a statistical distribution of a first or a higher order. The higher order can be achieved by using an Edgeworth expansion [2] or a sum of normal distributions.

In such a statistical distribution of a higher order not only do mean value and covariance have to be matched to comply with a quantity of data - as in the case of such a statistical distribution of the first order - but further higher-order parameters like moments and cumulants also have to be matched.

It should be noted that the possibilities mentioned for achieving a higher order without restricting the generality are only two selected statistical distributions. Other possibilities are known to persons skilled in the art.

In addition, in the sum of normal distributions, the individual normal distributions and thus indirectly the neuronal activities can be weighted.

Optimization can also be implemented by means of a maximum likelihood estimation [1] method.

In the optimization, a relationship between the linear statistical relationship and the statistical distribution can be taken into consideration as an auxiliary condition.

It is also expedient, because by this means the biological model of neuronal structures can be mapped in a more real way, for external influences on the signals to be taken into consideration in the linear statistical relationship. Such external influences may, for example, be sensory inputs of sensory cells on the examined areas.

The determination of signals in the invention, for example of BOLD signals, can be carried out by measuring signals or else by transferring and/or reading in existing signals.

The invention and further development described are particularly suitable for using in an fMRI technique, which is considerably improved and more powerful as a result.

In the context of such an fMRI use or fMRI examination, the neuronal areas are areas of the brain with corresponding nerve structures of patients to be examined and diagnosed.

In the fMRI examination using the inventive approach, BOLD signals are measured in various areas of the brain of a patient for defined perceptory or motor tasks carried out by the patient, which BOLD signals describe or represent the neuronal activities in the respective areas of the brain. These are evaluated or analyzed, whereby the signal coupling variables are determined.

Using the analysis results, in particular the signal coupling variables, functional as well as physical dependencies between areas of the brain can be detected and determined. These can further be used for a diagnosis concerning a functional disorder in an area of the brain of a patient, for example by comparing "disordered" dependencies with those of healthy persons.

An exemplary embodiment of the invention is explained below and shown in the Figures, in which

Figure 1 shows a device for carrying out an fMRI according to an exemplary embodiment,

Figure 2 shows a sketch containing steps in a method for analyzing BOLD signals according to an exemplary embodiment.

Exemplary embodiment: Functional nuclear spin tomography (fMRI)

Fig. 1 shows a device 100 for carrying out functional nuclear spin tomography or magnetic resonance tomography (abbreviated to fMRI) and a functional nuclear spin tomograph or magnetic resonance tomograph 100.

Basic principles of fMRI technology, which is a further development of the known magnetic resonance tomography, are known from [3].

The nuclear spin tomograph 100 has a closed tunnel 110 which is incorporated in a magnet 120 in such a way that this magnet generates a strong magnetic field in the tunnel 110.

The nuclear spin tomograph 100 also has a patient table 130 that can be introduced into the tunnel 110, on which table a patient is placed for an examination.

In addition, the nuclear spin tomograph 100 has a control unit 131 which enables monitoring and control of the patient table 130 in the examination, for example a controlled introduction of the patient table 130 into the tunnel 120.

As further components, the nuclear spin tomograph 100 has a measuring device 140 for the measurement of BOLD (Blood Oxygenation Level Dependent) signals, an associated evaluation device 141 for evaluating the measured BOLD signals, in this case a high-performance computer, as well as an operating or interaction device 142 for operating personnel and a display device 143 for displaying an examination result.

The components of the nuclear spin tomograph 100 are functionally connected to one another, for example via signal lines or data lines 150, via which the data and signals can be transferred.

Based upon the fMRI technique, the neuronal activity in areas of the brain of a patient can be measured and analyzed and a diagnosis derived from this by means of the functional nuclear spin tomograph 100 shown in Fig. 1.

To this end, the BOLD (Blood Oxygenation Level Dependent) signal in individual selected areas of the brain of the patient is measured by means of the measuring device 140, said BOLD signal being connected with the neuronal activity in the respective area.

The result of such fMRI measurements shows the curve of the activity of the individual areas over a certain period of time, for example during cognitive sequences as a result of specific perception processes or motor tasks which have to be carried out by the patient during an examination.

Functional disorders in the brain of the patient are thus implicitly contained in the measured fMRI signals.

Using the evaluation device 141, which makes available or implements a new method of analysis, the fMRI measurements, i.e. the BOLD signals measured in individual areas of the brain, are analyzed.

This new method of analysis represents in this case an improved further development of the known method of analysis described above.

In the new method of analysis, brain activity is determined in the form of corresponding activation patterns in the examined areas in the brain and/or relationships between activation patterns in the examined areas and from that conclusions drawn directly of functional disorders in the brain and their causes.

The new method of analysis made available by the evaluation device 140 is based upon an extended and more flexible model of the brain, of the neuron structures in the brain and their behavior, in

particular their interactions, on the basis of which the measured BOLD signal is analyzed and evaluated.

The basic principles of the new method of analysis and the model are explained below.

The results or the conclusions of an examination are shown on the display device 143 and can be further processed by means of the operating and interaction device 142 in connection with the evaluation device 141. They also serve as a basis for a medical diagnosis in respect of a patient to be examined and diagnosed.

Basic principles of the new method of analysis (Fig. 2, steps 210 to 250)

It is pointed out that the new method of analysis is an improved further development of the old method of analysis described above. Consequently, it is the case below that - unless stated otherwise - the old and new method of analysis match for these parts. Where matching parts are mentioned explicitly, they exhibit the labeling used previously hereinabove.

Using the new method of analysis 200 the fMRI measurements (210), i.e. the BOLD signals in examined areas of the brain of a patient, are analyzed (210 to 250) and/or compared with reference fMRI measurements. In this way, conclusions are drawn directly about functional disorders in the examined brain and their causes.

The new method of analysis 200, which generates statistical characteristic quantities, such as statistical correlations between fMRI measurements in various areas of the brain, is based upon an extended and more flexible mathematical model (220) of the brain based upon the known mathematical model according to (3).

In this extended model (220) of the new method of analysis, the coupling matrix S is populated in all (matrix)positions by changeable coupling strengths S_i.

In the new method of analysis 200 all - because they are also changeable - coupling strengths S_i are determined in such a way that statistical characteristic quantities which are determined from the fMRI measurements can best be explained (210 to 250).

A data point $s=s_t$ represents the totality of all the BOLD signals s1, ..., sN of the individual n examined areas at a point in time t (or averaged over a time interval t) (t=[1;T]).

The fMRI measurement comprises a large number of such data points s1, s2, ..., sT for differing perception processes and/or motor tasks for which the corresponding BOLD signals were measured.

In contrast to the old known method of analysis in which a multivariant standard distribution was assumed for the statistical distribution of the data points, in the new method of analysis 200 a weighted sum of normal distributions is assumed for the statistical distribution (220).

$$P(s \mid C_1,,C_L,\mu_1,\ldots\mu_L,\Sigma_1,\ldots,\Sigma_L)= \tag{5}$$

$$\frac{1}{\sum_{l=1}^{L} C_l} \bullet \sum_{l=1}^{L} \left\{ \frac{C_l}{\sqrt{2\pi}^N \bullet |\Sigma_l|} \bullet e^{-\frac{1}{2}(s-\mu_l)'\Sigma_l^{-1}(s-\mu_l)} \right\}$$

In this case, the chosen statistical distribution and thus also the equivalence of probabilities P=P(s|C1, ..., CL, μ1, ..., μL, Σ1, ..., ΣL) (230) (cf. (2)) for the occurrence of measured data points s1, s2, ..., sT depend on more or different parameters than the mean value μ and the covariance Σ of the old known method of analysis.

In the new method of analysis 200 specific statistical variables, which can be calculated for the chosen statistical distribution, are now correlated with the model parameters, i.e. the coupling strengths S_i, the mean value $\mu\varepsilon$ of external influence ε and the covariance $\Sigma\varepsilon$ of ε.

These include *inter alia* the means values $\mu 1$, ..., μL, the covariances $\Sigma 1$, ..., ΣL and all the moments and cumulants of the chosen distribution of a higher order.

An implicit relationship between the statistical distribution parameters and the model parameters to be determined emerges from this, in this case taking into consideration the distribution (5) and the extended model based upon the model according to (3).

$$\mu = \mu(C_1, C_L, \mu_1, ..., \mu_L, \Sigma_1, ..., \Sigma_L)$$

$$\Sigma = \Sigma(C_1, ..., C_L, \mu_1, ..., \mu_L, \Sigma_1, ..., \Sigma_L)$$

$$\vdots$$

$$\mu = \mu(S, \mu_\varepsilon, \mu)$$

$$\Sigma = \Sigma(S, \Sigma_\varepsilon \Sigma) \qquad (6)$$

In conformance with the old known method of analysis, the optimum model parameters are now determined (240) in an analogous manner in the new method of analysis 200 using maximum likelihood estimation [1] through optimization or maximization of the probabilities (5).

The basic principles of maximum likelihood estimation are described in [1].

The parameters to be taken into consideration for the optimization are the parameters of the chosen statistical distribution of a higher order, in this case the weighted sum of normal distributions,

the desired model parameters and statistical variables, in this case the mean value μ and the covariance Σ from (6), via which the relationships between the model parameters and the statistical distribution (5) were produced.

These relationships from (6) must be taken into consideration as auxiliary conditions in the optimization.

The optimization then leads to the desired coupling strengths S_i which describe dependencies between the BOLD signals (250) and form the basis of the further evaluation and medical diagnosis (250).

An alternative to the exemplary embodiment described is indicated below.

In place of the weighted sum of normal distributions, the distribution of data points can also be described by an Edgeworth expansion.

The basic principles of the Edgeworth expansion are described in [2].

The following publications are cited within the context of this document:

[1] T.W. Anderson, An Introduction to Multivariable Statistical Analysis, Chapter 3, John Wiley & Sons, Inc., New York, London, Sydney, 1994

[2] Samuel Kotz, Norman L. Johnson (Editors-In-Chief), Cornish-Fisher and Edgeworth Expansions, Ch. 4, pages 188-192, Encyclopedia of Statistical Sciences, Volume 2, John Wiley & Sons, 1982

[3] A. W. Toga and J. C. Maziotta (Ed.), "Brain Mapping: The Methods", Ch 9: M. S. Cohen: "Rapid MRI and Functional Applications", Academic Press 1996

[4] Specification for "fmri.pro" software relating to quantitative fMRI analysis, obtainable on 07.09.2001, under http://www.med.uni-muenchen.de/radin/html/arbeitsgruppen/fmri/ccfmri.html

[5] Specification of fMRI - device, obtainable on 07.09.2001, under http://www.unipublic.unizh.ch/campus/uni-news/2001/0147/fmri.html

[6] A.R. McIntosh et al., Structural Equation Modeling and Its Application to Network Analysis in Functional Brain Imaging, Human Brain Mapping, 2:2-22, 1994.